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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,534	COLEMAN ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-75,87-92 and 99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-75,87-92 and 99* _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

This action is written in response to applicant's correspondence submitted 6/20/2003 in response to the office's first action on the merits sent out 1/15/2003, Claims 57, 72-75, 87, and 89-92 have been amended, claims 76-86, 93-98, and 100 have been canceled, and no new claims have been added. Claims 57-75, 87-92, and 99 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is non-final.**

Priority

Acknowledgement of the now abandoned, parent application, 09/178,170 filed 10/23/1998 and of the provisional application 60/063,274 filed 10/24/1997 from which it claims benefit has been made. The filing date of the instant claims is deemed to be the filing date of the provisional application, 10/24/1997.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 57, 58, 59, 60, 61, 62, and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheetham et al.(Society for Neuroscience, Vol. 22, 1996).

With regard to claim 57, Cheetham et al. teach a method for creating a gene profile for a given stage of Alzheimer's disease, the method comprising:

(a) providing, from a "diseased brain(such as one suffering from Alzheimer's Disease)"(line 1), a plurality of cells, the cells of the plurality characterizing a stage of disease progression;

(b) isolating mRNA from cells in the plurality to produce a heterologous population of mRNAs(line 9); and

(c) determining the levels of expression of the mRNAs of more than one gene in the population of mRNAs, wherein the levels of expression constitute a gene profile for the given stage of Alzheimer's disease(lines 15-16).

With regard to claim 58, Cheetham et al. teach the above method wherein step (c) comprises producing antisense RNA transcripts from the population of mRNAs and amplifying the antisense RNA transcripts(lines 11-14).

With regard to claim 59, Cheetham et al. teach the above method wherein the antisense RNA transcripts are quantitated, after amplification, by: using the aRNA probe for a reverse northern blot(lines 13-14).

With regard to claims 60, 61, and 62 Cheetham et al. teach the above method wherein the "different expression profiles between NFT-bearing and NFT-free neurons will be

presented"(lines 15-16) and thus the stage through their methodology that allows Cheetham et al. to "characterize individual cells by ICC using antibodies to identify their neurofibrillary tangle(NFT) bearing status"(lines 6-7).

With regard to claim 63, Cheetham et al. teach the above method wherein the stage of Alzheimer's disease is determined by obtaining neuronal cells from the patient and exposing at least one of the neuronal cells to "antibodies"(line 7 and lines 1-2).

2. Claims 57, 58, 59, 67, 87, 88, and 99 are rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al.(Neuroscience, Vol. 60, 1994).

Applicant should note that the examiner is interpreting "gene profile" as "mRNAs of more than one gene" absent any definition or guidance in the specification as to the breadth included in the recitation of "gene profile".

With regard to claim 57, Murray et al. teach a method for creating a gene profile for a given stage of Alzheimer's disease, the method comprising:

(a) providing, from a patient who has Alzheimer's disease, a plurality of cells, the cells of the plurality characterizing a stage of disease progression;

(b) isolating mRNA from cells in the plurality to produce a heterologous population of mRNAs(Pg. 38); and

(c) determining the levels of expression of the mRNAs of more than one gene in the population of mRNAs, specifically of BDNF(brain-derived neurotrophic factor) and CamII Kinase, wherein the levels of expression constitute a gene profile for the given stage of Alzheimer's disease(Pg. 37).

With regard to claim 58, Murray et al. teach the above method wherein step (c) comprises producing antisense RNA transcripts from the population of mRNAs and amplifying the antisense RNA transcripts(Pg. 38 left column).

With regard to claim 59, Murray et al. teach the above method wherein the antisense RNA transcripts are quantitated, after amplification, by (a) hybridization with cDNA using the cRNA probes and antisense RNA probes(Pg. 38).

With regard to claims 67 and 88, Murray et al. teaches the above method wherein the mRNA isolated encodes a kinase(CamII Kinase).

With regard to claim 87, Murray et al. teach the above method with a final step of comparing two gene profiles of a diseased patient and of another individual in their assertion that they found "reduced levels of BDNF mRNA and increased levels of mRNA encoding the alpha subunit of Cam II kinase in Alzheimer's disease as compared to matched control hippocampal tissues"(Pg. 42 and figure 5).

With regard to claim 99, Murray et al. teach a method for determining whether a compound affects the gene profile for a given stage, following the treatment of one patient and the absence of treatment for another and the final step of comparing the results in their teaching that following "kainate administration mRNA levels are increased strikingly within the adult forebrain"(Pg. 44). Furthermore they teach that "treatments with agents that reduce basal level activity (i.e. benzodiazepines) reduce BDNF mRNA levels" while "in contrast to these findings CamII kinase mRNA levels decrease"(Pg. 44).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 60-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al.(Neuroscience, 1994) in view of Ikeda et al. (Human Pathology, 1990).

With regard to claim 57, Murray et al. teach a method for creating a gene profile for a given stage of Alzheimer's disease, the method comprising:

(a) providing, from a patient who has Alzheimer's disease, a plurality of cells, the cells of the plurality characterizing a stage of disease progression;

(b) isolating mRNA from cells in the plurality to produce a heterologous population of mRNAs(Pg. 38); and

(c) determining the levels of expression of the mRNAs of more than one gene in the population of mRNAs, specifically of BDNF(brain-derived neurotrophic factor) and CamII Kinase, wherein the levels of expression constitute a gene profile for the given stage of Alzheimer's disease(Pg. 37).

With regard to claim 58, Murray et al. teach the above method wherein step (c) comprises producing antisense RNA transcripts from the population of mRNAs and amplifying the antisense RNA transcripts(Pg. 38 left column).

With regard to claim 59, Murray et al. teach the above method wherein the antisense RNA transcripts are quantitated, after amplification, by (a) hybridization with cDNA using the cRNA probes and antisense RNA probes(Pg. 38).

With regard to claims 67 and 88, Murray et al. teaches the above method wherein the mRNA isolated encodes a kinase(CamII Kinase).

With regard to claim 87, Murray et al. teach the above method with a final step of comparing two gene profiles of a diseased patient and of another individual in their assertion that they found "reduced levels of BDNF mRNA and increased levels of mRNA encoding the alpha subunit of Cam II kinase in Alzheimer's disease as compared to matched control hippocampal tissues"(Pg. 42 and figure 5).

With regard to claim 99, Murray et al. teach a method for determining whether a compound affects the gene profile for a given stage, following the treatment of one patient and the absence of treatment for another and the final step of comparing the results in their teaching that following "kainate administration mRNA levels are increased strikingly within the adult forebrain"(Pg. 44). Furthermore they teach that "treatments with agents that reduce basal level activity (i.e. benzodiazepines) reduce BDNF mRNA levels" while "in contrast to these findings CamII kinase mRNA levels decrease"(Pg. 44).

Murray et al. do not teach obtaining neuronal cells and viewing NFTs through a microscope to determine if the cells are filled with neurofibrillary tangles(NFT) that are not frank.

However, Ikeda et al. teach microscopic examination of "case no.1" that revealed a decreased number of neurons with a diffuse distribution of senile plaques and neurofibrillary

tangles(NFTs). The abundance of NFTs in the brain of case no. 1 is "consistent with a diagnosis of AD...furthermore, on the basis of all the clinical and pathologic information, this case is considered to be AD at an advanced stage"(1224). Case 2 represented an example of an early stage of AD(probable familial)"Additionally, a very small number of neurofibrillary tangles was seen in the neocortical sections, but the diencephalons and cerebellum did not show any significant lesions"(1223) in "case no.2". The reference teaches that "these findings suggest that case no. 2 might be an example of AD at a very early stage, with pathologic changes that would eventually develop into a picture similar to that of case no.1 with advanced AD having many typical or classical senile plaques"(1224).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murray et al. so as to have provided an additional process for the detection or diagnosis of Alzheimer's involving observing NFT, in a stage-dependent configuration, under the microscope.

4. Claims 63 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al.(Neuroscience, 1994) in view of Callahan et al. (Neurobiology of Aging, 1994) and in further view of Ghanbari et al. (US 5,811,310).

The teachings of Murray et al. can be referenced from the above rejection of claims 60-62.

Murray et al. do not teach determining the stage of Alzheimer's by obtaining neuronal cells and exposing at least one of the neuronal cells to two or more antibodies wherein the antibodies comprise: an anti-TG-3 and mAb69; or an anti-MC-1 and mAb69.

However, Callahan et al. does teach determining the stage of Alzheimer's by obtaining neuronal cells and exposing them to two or more antibodies wherein the antibodies comprise: mAb69 and biotinylated horse antimouse(382). Callahan et al. further teach that "end-stage Alzheimer's disease cases demonstrated sparse grain density for GAP-43 probe over tangle-bearing neurons"(Fig. 1a and b). While in neurons partially filled with NFT, "grains appeared to be equally probably over NFT vs. over NFT-free regions of the cell"(Fig 1c). The reference teaches the use of mAb69 as a marker of frank NFT formation as seen in for example in Fig.1 when "parahippocampal gyrus sections reacted with mAb69 for PHF-tau", a conformational epitope in NFT(383).

Callahan et al. do not teach determining the stage of Alzheimer's by obtaining neuronal cells and exposing at least one of the neuronal cells to two or more antibodies wherein the antibodies comprise: an anti-TG-3 and mAb69; or an anti-MC-1 and mAb69 together.

However, Ghanbari et al. teach the use of an antibody, ALZ-50, whose action is analogous to that of mAb69 and whose action is taught to be coupled with the use of the claimed MC-1 and TG3. Ghanbari et al. teach that ALZ-50 reacts with normal and recombinant(abnormally phosphorylated) Tau from human origin. Ghanbari et al. teach several antibodies that show reactivity to human tau either through non-specific cross-reactions with normal and abnormally phosphorylated tau or because they recognized specific epitopes on normal and abnormal phosphorylated tau. Ghanbari also reiterates that in the art many antibodies to specific phosphorylation sites and conformations of tau have been combined in double immunocytochemistry(ICC) experiments. The reference further teaches that it is typical that in the ICC one of the reactions is specifically used for neurofibrillary tangles(NFT). ALZ-

50 then is seen as an analogous, specifically for NFT, component of the double ICC being taught in the Ghanbari patent. Ghanbari et al. further teaches the advantage of using MC1 and TG-3 in addition to ALZ-50 as "ALZ-50 only reacts with the Alzheimer antigen, the TG-3 epitope can be generated on recombinant tau by appropriate phosphorylation, and its reactivity against the Alzheimer antigen is vastly greater than with phospho recombinant tau"(Col. 10, lines 2-7). The reference continues to teach that, "some recognize epitopes that are discontinuous (ALZ-50, MC1), while others bind to epitopes that are both discontinuous and phosphorylation dependent(TG-3)"(Col. 10). The reference explains that for these reasons, "the lower reactivity of the antibodies with normal brain proteins is not problematic because a differential in antibody reactivity exists in AD due to the formation of the highly reactive Alzheimer antigen"(Col. 10, lines 15-19). In the end, as there exists a wide variety of monoclonal antibodies that are capable of staining the NFT when viewed under the microscope, the prospect of interchanging mAb69 for ALZ-50 in an ICC experiment would be a basic change to well established AD dogma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murray et al. so as to have provided as step for determining the stage of Alzheimer's by obtaining neuronal cells and exposing at least one of the neuronal cells to two or more antibodies wherein the antibodies comprise: an anti-TG-3 and mAb69; or an anti-MC-1 and mAb69, as such a detection of NFT is standard protocol in evaluating AD ICC experiments and the use of such antibodies are typical of AD detection.

5. Claims 66, 71, and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al.(Neuroscience, 1994) in view of Cataldo et al. (Neuron, 1995).

The teachings of Murray et al. can be referenced from the above rejection of claims 60-62.

Murray et al. do not teach the above method for creating a gene profile wherein the mRNA isolated in step(b) comprises mRNA that encodes a lysosomal hydrolase or cell stress related protein.

However, Cataldo teaches that "the mRNA for cathepsin D was increased in AD brain in pyramidal neurons of which a majority appeared histologically normal"(Pgs. 671-680).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murray et al. so as to have included the lysosomal hydrolase and cell stress related protein, cathepsin D of Cataldo in the gene profile for the expected benefit of creating a more informative method as the detection of the expression of this cathepsin mRNA is characteristic of an Alzheimer diseased(AD) brain.

6. Claims 70 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al.(Neuroscience, 1994) in view of Chandrasekaran et al.(Molecular Brain Research, 1994).

The teachings of Murray et al. can be referenced from the above rejection of claims 60-62.

Murray et al. do not teach the above method for creating a gene profile wherein the mRNA isolated in step(b) comprises mRNA that encodes a mitochondrial protein.

However, Chandrasekaran teaches that "a decrease of mRNA for mitochondrial-encoded cytochrome oxidase (COX) subunits I and III" is observed in an AD brain(Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Murray et al. so as to have included the mitochondrial-encoded cytochrome oxidase (COX) subunits I and III of Chandrasekaran in the gene profile for the expected benefit of creating a more informative method as the detection of the expression of this COX I and III mRNA is characteristic of an Alzheimer diseased(AD) brain.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 57-75, 87-92, and 99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for creating a gene profile of late stage Alzheimer's disease(AD) from biopsied AD brain tissue's cells using the detection of decreased level of expression for the messages that encode cyclin D1, HSP27, and GAD and an increased level of expression for the messages that encode α1-ACT, and weel all 5 values determined in comparison to a control, the specification does not reasonably provide enablement for a method wherein;

1) Any given stage other than late stage of AD is determined by the gene profile.

2) Any increase or decrease in any given gene not previously associated with AD is detected by the gene profile.

3) Any sample source other than brain tissue is used for creating a gene profile.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 57-75, 87-92, and 99 are broadly drawn to a method for creating a gene profile for any stage of Alzheimer's disease, the method comprising providing from a living patient who has AD, a plurality of cells from any source other than brain tissue, the cells of the plurality characterizing any stage of disease progression; isolating mRNA from cells(harvested from any bodily source other than brain tissue) in the plurality to produce a heterologous population of mRNAs; and determining the levels of expression of the mRNAs of all genes in the population of mRNAs, wherein the levels of expression constitute a gene profile for any stage of Alzheimer's disease and further to a method of determining whether a compound affects the gene profile for any stage of Alzheimer's disease. The specification teaches on page 54 that "it was found that the expression levels of cyclin D1, HSP27, and GAD were significantly decreased in late stage AD samples and that expression of α1-ACT and weel were increased". However, the specification then goes on to teach that the present invention provides the ability to create a gene profile wherein the messages are derived from cells of cerebrospinal fluid, blood, saliva, urine, cheek scrapings or skin(Pg. 27). The specification further recites that mRNA encoding all cell cycle regulators, lysosomal hydrolases, kinases, phosphatases, apoptotic factors,

mitochondrial proteins, and cell-stress related proteins are enabled to be practiced within the above mentioned, broadly drawn method. However, as will be further discussed, there is no support in the specification and prior art for these secondary and tertiary embodiments besides just the specific 5 genes whose expression had been taught. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites many studies in the prior art whose focus has "been limited to examining only one or a few messages at a time by *in situ* hybridization"(Pg. 18). The art also teaches the use of Northern Blot Analysis to quantify the changes of RNA transcripts in AD(Chandrasekaran, K Mol Brain Res. 1994). However, there is no evidence that this method of gene profiling would be operable. It is unpredictable, for example, that a profile consisting of an array that every gene on that array would prove to be informative, ie. their expression would prove to have a statistically significant value. The post filing date art supports the unpredictability inherent in such a task in Hata et al.'s teaching of a cDNA microarray that attempts to analyze the expression of more than 8000 genes. Hata et al. use this technology in hopes of comparing gene expression in the hippocampus containing neurofibrillary tangle-associated lesions from an Alzheimer's disease patient to expression from the parietal cortex of the same patient that lacked these lesions(Biochemical and Biophysical Research Communications 284, 310-316, 2001). However, out of the 8000 genes analyzed, only 20 were found to be "significantly up-regulated", roughly .25%. Furthermore, out of the .25% found to be "significant" only a handful appear to be known or possibly relevant players in the AD system. This post filing date art aptly relays the great unpredictability of detecting the statistically relevant expression of such a large population of genes taking into account the many

variables associated in the array techniques and Alzheimer disease paradigm. The specification after all, teaches only 5 statistically significant values harvested from their practice of the method and all of them are characteristic to only the "late stage" of AD progression, not any given stage. It is then highly unpredictable as shown in the prior and post filing date art to practice this method as it is broadly claimed.

There is also a great deal of unpredictability in the assumption that it is possible to create a gene profile wherein the mRNA messages are derived from cells of cerebrospinal fluid, blood, saliva, urine, cheek scrapings or skin(Pg. 27). Both the specification and art teach methods wherein the sample cell is isolated from a post-mortem AD brain tissue but none teach the ability isolate messages from cerebrospinal fluid, blood, saliva, urine, cheek scrapings or skin(Pg. 27). The specification and art are both silent in the enablement of these particular embodiments. The art teaches that detection of diseases can occur in bodily fluids that have previously in their circulation, physically come into contact with the diseased tissue(Ralph et al. US Patent 6190857). The art is void however, of the prophetic embodiment of obtaining mRNA messages relevant to a diseased portion of an AD brain within for example, cheek scrapings. As a result, the prior art does not provide any guidance with regard to the identification of nucleic acids which are isolated from cells that originate in a location distant from the point of AD. Additionally, the art attests to the difficulty of AD diagnosis, and the teaching that the confirmation of such a diagnosis is currently only possible post-mortem. Buckland et al. studied levels of amyloid precursor protein mRNA in blood cells of AD patients but did not observe any differences between disease and control groups(Molecular Brain Research, 1993). Sato et al. showed that Cu, Zn superoxide dismutase mRNA levels were higher in patients with AD than in skin fibroblast samples(Acta Neurol. Scand 1995:91:165-168). However, they do not suggest any other transcripts in skin fibroblasts that might be useful for the diagnosis of AD, and all of

the current claims require that "more than one gene" be detected. The identification of such other transcripts is highly unpredictable.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to profiles of genes whose putative expression is correlated to a certain(not presently apparent) stage of AD. Not only will the receipt of statiscally relevant expression information for all genes associated with AD require much work, but also the ability to derive such information from mRNA encoding all cell cycle regulators, lysosomal hydrolases, kinases, phosphatases, apoptotic factors, mitochondrial proteins, and cell-stress related proteins. Not to mention the amount of work associated with the detection, if at all possible, of mRNA messages in bodily fluids and tissue that is located distant to the AD brain tissue. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of any profile consisting of data that reveals a correlation of more than one gene to any given stage in Alzheimer's Disease, let alone all of those claimed in that are mRNA encoding all cell cycle regulators, lysosomal hydrolases, kinases, phosphatases, apoptotic factors, mitochondrial proteins, and cell-stress related proteins in vivo site directed mutagenesis using an oligonucleotide-mutagen complex. Lastly, not a single working example is present illustrating the practice of the method wherein any sample other than post-mortem brain tissue is used and from which mRNA messages are harvested.

Guidance in the Specification.

The specification teaches on page 54 that "it was found that the expression levels of cyclin D1, HSP27, and GAD were significantly decreased in late stage AD samples and that expression of α1-ACT and weel were increased". The specification provides no evidence that the disclosed method was capable of being practiced to the full extant that it is broadly claimed. The specification teaches only that 5 statistically relevant genes were found in their attempt to discover an entire profile, characteristic of given stages. The specification also only teaches the isolation of mRNA messages from post-mortem brain tissue, and is silent to the practice of the method wherein any other bodily fluid or body tissue is used. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that based on seminal stage, statiscal tests using univariate and multivariate considerations as applied to control populations, a profile is probably possible to create. No reduction to practice is taught though by the specification that give guidance in order to practice the invention as currently claimed.

Level of Skill in the Art

The level of skill in the art is deemed to be high, but the unpredictability associated with identifying isolated selected mRNA messages from bodily fluids and tissues that have not contacted the point of disease and are useful for the detection of diseases is higher. The human blood, for example, expresses hundreds of thousands of different messages, and which of these particular messages would be useful for the detection of Alzheimer's disease is highly unpredictable. The determination of such an association requires extensive laboratory work as is exemplified by the teachings of Ralph et al.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where gene profiles do not necessarily produce statistically relevant data and instead depend upon numerous known and unknown parameters such as the how changes in expression of certain genes relate to the pathogenesis of AD, how an entire class of proteins can be necessarily detected as messages involved in AD, or how messages can be obtained from sites distant AD brain tissue, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the present method for creating a gene profile as broadly claimed (i.e encompassing a method wherein any and all genes are isolated and correlated to any and all stages of AD). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris
10/7/2003

JEFFREY FREDMAN
PRIMARY EXAMINER